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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/556,901	02/02/2006	Mark Ashton	BJS-620-401	1869

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EXAMINER
CHANDRAKUMAR, NIZAL S

ART UNIT	PAPER NUMBER
1625	

MAIL DATE	DELIVERY MODE
12/21/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/556,901	ASHTON ET AL.	
	Examiner	Art Unit	
	Nizal S. Chandrakumar	1625	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-4,6-9,11-20,22-29,31,34-39,41-48 and 50* is/are pending in the application.

4a) Of the above claim(s) *1-4, 6-9, 11-20, 22-29* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *31,34-48 and 50* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Applicants response filed 11/21/2007 is acknowledged.

Applicants amended the claims.

Formal Matters:

Claims 1-31 were indicated in the office action filed Aug 23 2007 as withdrawn from consideration because they were drawn to non-elected invention.

After entry of the amended claims, claims 1-4, 6-9, 11-20, 22-29, 31, 34-39, 41-48 and 50 are pending. Of these,

claims 1-4, 6-9, 11-20, 22-29 are pharmaceutical method claims;

claim 31 is pharmaceutical composition claim;

claims 34-39, 41-48 and 50 are compound claims.

In the present list of claims 5, 10, 21, 30, 32-33, 40 and 49 are cancelled.

Compound and composition claims 31, 34-39, 40-48 and 50 are under prosecution.

Method claims 1-4, 6-9, 11-20, 22-29 will be rejoined when the compound and composition claims become allowable.

The Examiner acknowledges that the claims 1 had been withdrawn from consideration and claim 1 does not recite the objected-to term (i.e., "solvate").

Response to Applicants Remarks to claim rejections:

Claim Rejections - 35 USC § 112 (second paragraph)

Applicants presumption with regards to what claim is being rejected under Claim Rejections - 35 USC § 112 is correct and is appreciated in view of the typographical error on the

part of the Examiner. Claim 34 is being rejected under 35 USC § 112 (second paragraph) because the limitation 'solvate' claim 34 does not define what the chemical structure of the solvates are.

Applicants defines solvates as a complex of the compound or a salt thereof and a solvent as per the specification. Solvated compound should have a defined, definite chemical composition (such as monohydrate, 0.75 CH3OH etc.).

Applicants state that compounds are regularly defined in US Patent claims as including solvates. What is allowed in the issued US patent data base is of no consequence to prosecution at hand. Each patent application is evaluated based on what is claimed and what is the enabled subject matter.

As such the rejection of claim 34 under 35 USC § 112 (second paragraph) is maintained.

Claim Rejections - 35 USC § 112 (scope of enablement)

The applicant accepts that the amount of experimentation must not be unduly extensive. As exemplified in the previous office action, it is the Examiner's position as the applicant correctly understands it (page 15, line 4-5 of applicants remarks), based on the direction and working example present in the specification, undue experimentation would be needed to practice the invention commensurate with the scope of the claims. The claims are drawn to substitutions layered on top of substitutions and attempts to address the feasibility issues relating to each one of the these billion possibilities would require undue burden on the Examiner. The Examiner reiterates that only examples were provided in the previous office action to illustrate lack of enablement in the specification.

With regards to the number of laundry list of substituents and the enabling examples of two compounds present in the specification, the applicant's arguments and the cited case laws were carefully considered. Contrary to applicant's statement with regards to 'specific problem identified in the art.....' (page 15 line 6-7 of the response), the examiner provided specific technical problems that would be faced with one or ordinary skill in the art (see previous office action, pages 6 and 7 relating to differentiation of similar functionalities, Pd-insertion on similar C-halogen bonds, etc).

With regards to breadth of the claims, the applicant reminds the Examiner that 'many compound claims are granted where the claims cover a seemingly endless possibility of compound structures'. It is the Examiners position that what has been granted in the past is irrelevant to the prosecution at hand. Patentability would be based on enabling disclosure of the instant application.

With regards to level of skill in the art, the applicant states 'that it is a misjudgment of the examiner to rely on the unpredictability in the art of organic synthesis'. One of the premises of publications such as "Organic Synthesis", is the applicability of standard organic procedures for specific particular components.. Most if not all journals relating to making of compounds require the presence of 'Experimental Section' or 'Supplementary Material' detailing chemical reactions even of mundane nature. This is because of the art recognized unpredictability of known chemical transformations. As stated earlier, the level of skill in the art is high, but the issue at hand is undue burden to practice the invention.

With regards to the amount of direction and or guidance present, the applicant statement is correct with respect to the examiner's position. At this point, the Examiner is concerned with (1) the makeability of the elected group of compounds without undue research burden (2) whether

adequate direction and guidance is present in the specification (3) whether the applicant had possession of at least a few representative samples of the multitude of claimed formulae . Citations of organic chemistry text books is no substitute for requirement of direction and guidance in the specification relevant to claims of the elected group.

The Applicant requests the Examiner to see the compounds in Table 4. It is/was the Examiner's contention that these examples are irrelevant to the chemistry required for making the elected group of compounds. The only commercial compound of relevance to the present discussion is compound#3. Again, it is the position of the Examiner, that there is very little 'similarity' of this compound and those of the elected invention.

The applicant states that the Examiners conclusions with regards the variables do not recognize the degree to which the examples of the application are generally applicable to the claims. This is contrary to the statement present in the previous office action, for instance, with regards to the introduction of the mandatory 'hydroxamic acid' functionality. Thus, to derivatize the above-cited commercial compound#3, that is to introduce the acylated hydroxamic acid functionality at a specific position, the position dictated by the pharmacophore *(undisclosed in the specification)* necessary for binding, would require undue experimentation, because the teaching present in the specification is only for N-alkylation of a highly reactive (benzylic) halide. The acylation of nucleophiles (page 19 , line 3) to make N-acylhydroxamic acid is not teaching bond formation between aryl-C (or alkyl-C) and N of NHOH or its protected equivalent.

As to the lack of citation with respect to starting materials applicants arguments are not persuasive. The examiner agrees that given 'enough time and effort' any organic compound can be made, the questions is whether undue experimentation is needed. The applicant repeatedly asserts the availability of standard organic text books and commercial sources in lieu of the lack of direction and guidance in the specification. However in response to the Examiner's citation of

hydrogenation reaction as one of the many possible organic transformations that may be required to make some of the plethora of substituents claimed, the applicant states that hydrogenation was not suggested in the specification.

Applicants states that the claimed compounds are viable 'with reasonable experimentation' (such as reversing the nature of coupling partners in a Suzuki coupling) as a matter of routine planning. Even with the reversal of partners, the selective functionalization of the two partners, to set up the *particpiating* functional groups, would still exist. There is substantial gap between what is taught and what is claimed; what is needed is not reasonable experimentation, but undue experimentation.

In lieu of a description of a pharmacophore, the claims/specification are drawn to, three structural elements, a sulfur substituted benzene ring, a carboxylic acid moiety and a N-acyl-hydroxamic acid unit that could be joined in billion different ways, with linker moieites differing extensively in size, shape and functional groups. The two ways (i.e., two working examples) of connecting these three moieties illustrated in the specification provided compounds that have questionable biological activity (IC50s of 2 and 10 micormolars and inactive in cell assays (see previous office action, page 7). In spite of presumable Pk/PD properties of these two, what would be a pharmaceutical dosage for tumor regression with this biochemical profile?

Applicant's assumption as to the state of the art in chemistry is such that all chemical syntheses would be feasible with reasonable experimentation. The Examiner position pertaining to what is enabled in the instant specification is more along the lines of Dorwald et al. who states, "Most non-chemists would probably be horrified if they were to learn how many attempted syntheses fail, and how inefficient research chemists are. The ratio of successful to unsuccessful chemical experiments in a normal research laboratory is far below unity, and synthetic research chemists, in the same way as most scientists, spend most of their time working out what went wrong, and why. Despite the many pitfalls lurking in organic synthesis, most organic chemistry textbooks and research articles do give the impression that organic reactions just proceed smoothly and that the total synthesis of complex natural products, for instance, is maybe a labor-

intensive but otherwise undemanding task. In fact, most syntheses of structurally complex natural products are the result of several years of hard work by a team of chemists, with almost every step requiring careful optimization. The final synthesis usually looks quite different from that originally planned, because of unexpected difficulties encountered in the initially chosen synthetic sequence. Only the seasoned practitioner who has experienced for himself the many failures and frustrations which the development (sometimes even the repetition) of a synthesis usually implies will be able to appraise such work.....Chemists tend not to publish negative results, because these are, as opposed to positive results, never definite (and far too copious) [preface].....even structurally simple compounds often turn out not to be so easy to make as initially thought. [pg. 2]..... As illustrated by the examples discussed below, a good retrosynthesis requires much synthetic experience, a broad knowledge of chemical reactivity, and the ability to rapidly recognize synthetically accessible substructures [pg. 3]..... As will be shown throughout this book, the outcome of organic reactions is highly dependent on all structural features of a given starting material, and unexpected products may readily be formed. [8].....Even the most experienced chemist will not be able to foresee all potential pitfalls of a synthesis, specially so if multifunctional, structurally complex intermediates must be prepared. The close proximity or conformational fixation of functional groups in a large molecule can alter their reactivity to such an extent that even simple chemical transformations can no longer be performed. Small structural variations of polyfunctional substrates might, therefore, bring about an unforeseeable change in reactivity [pg. 9]....." Dorwald F. A. Side Reactions in Organic Synthesis, 2005, Wiley: VCH, Weinheim pg. IX of Preface pg. 1-15.

With regard to the 'use' aspect of the invention, the applicant maintains that 2 and 10 micromolar IC50s as showing of ability to inhibit glyoxalase I. The applicant states that one of ordinary skill is entitled to take from this result the knowledge that this type of compound has inhibitory activity. First, even one assumes 2 and 10 micromolar IC50s are result of ligand-active site interaction, that is, are not reflective of non-specific binding (given the absence of activity in cell assays), the

two compounds could hardly be considered as having a "type of structure", that is, defining a pharmacophore). This is especially because of the wide diversity of structural types encompassed by the elected group of compounds. The above-indicated three structural elements could be linked in billion different ways to produce compounds with widely differing molecular topography, size and weight. **Genentech Inc. v. Novo Nordisk A/S (CA FC) 42 USPQ2d 1001, states, "a patent is not a hunting license. It is not a reward for search, but compensation for its successful conclusion" and "[p]atent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable".**

To reiterate, it is the Examiner's position that the specification, at the time the application was filed, would not have taught one skilled in the art how to make and or use the full scope of the claimed invention without undue experimentation.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The previously rejected claims 34-50 now (after inclusion of the pharmaceutical composition claim 31) correspond, after amendment, to claims *31,34-48 and 50.* As such *31,34-48 and 50 are rejected* under 35 U.S.C. 112, first paragraph for reasons of record in office action filed 08/23/2007. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and or use the invention commensurate in scope with these claims.

No claim is allowed.

Applicant's arguments are not persuasive and the previously presented lack of enablement rejection is maintained. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Nizal S. Chandrakumar whose telephone number is 571-272-6202. The examiner can normally be reached on 8.30 am - 5 pm Monday- Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Janet Andres can be reached at 571-272-0867 or Primary Examiner D. Margaret Seaman can be reached at 571-272-0694. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would

like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Nizal S. Chandrakumar

D. MARGARET SEAMAN
PRIMARY EXAMINER